

Appl. No. 10/622,010  
Supplemental Response and Amendment to Office Action dated August 22, 2005

### AMENDMENTS TO THE CLAIMS:

Please amend the claims as shown below. This listing of claims will replace all prior versions and listings of claims in the application. Deletions of text are indicated with ~~strikethrough~~. Added text is shown underlined.

1. (currently amended) A method for screening a compound library to identify a compound with a physiological effect on a biological sample, the method comprising:
  - (a) contacting a plurality of biological samples with a plurality of members of a compound library;
  - (b) obtaining an expressed RNA sample from each of the plurality of biological samples;
  - (c) arraying a plurality of nucleic acids corresponding to the plurality of expressed RNA samples to produce a nucleic acid array, wherein said plurality of nucleic acids is selected from:
    - (i) total cellular RNA derived from said biological samples;
    - (ii) mRNA derived from said biological samples;
    - (iii) cDNA derived from said expressed RNA sample;
    - (iv) nucleic acids amplified from (i), (ii) or (iii);
  - (d) hybridizing a plurality of defined sequence probes, which probes each comprise a different polynucleotide sequence, and which probes are each capable of generating a different detectable signal, to the nucleic acid array;
  - (e) quantitating a signal corresponding to hybridization of each of the plurality of defined sequence probes to the nucleic acid array, thereby generating a quantitated hybridization signal; and,
  - (f) detecting at least one quantitated hybridization signal that differs from a control hybridization signal, thereby identifying a compound that exerts a physiological effect on a biological sample; and,
  - (g) entering the quantitated hybridization signal into a database.

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2. (original) The method of claim 1, wherein each of the plurality of biological samples is contacted with a different member of the compound library.
3. (original) The method of claim 1, wherein the control hybridization signal is produced by:
  - (i) providing a nucleic acid array comprising a plurality of control nucleic acids obtained from a control biological sample;
  - (ii) hybridizing the plurality of defined sequence probes to the nucleic acid array comprising the control nucleic acids; and,
  - (iii) detecting a control hybridization signal.
4. (original) The method of claim 3, wherein the control nucleic acids comprise amplification products.
5. (previously presented) The method of claim 3, wherein the control biological sample comprises an untreated biological sample or a 0 time point sample.
6. (original) The method of claim 1, wherein the quantitated hybridization signal differs qualitatively or quantitatively relative to the control hybridization signal.
7. (original) The method of claim 1, wherein the quantitated hybridization signal is increased or decreased relative to the control hybridization signal.
8. (original) The method of claim 1, comprising detecting the quantitated hybridization signal that differs from a control hybridization signal by performing at least one statistical analysis.
9. (original) The method of claim 1, wherein the quantitated hybridization signal is increased or decreased at least one standard deviation relative to the control hybridization signal.
10. (original) The method of claim 1, wherein the quantitated hybridization signal is increased or decreased at least two standard deviations relative to the control hybridization signal.

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11. (original) The method of claim 1, comprising providing a plurality of nucleic acid arrays.
12. (original) The method of claim 1, wherein the biological samples comprise one or more of: a tissue, a tissue extract, a primary cell isolate and cells grown in culture.
13. (original) The method of claim 1, wherein the biological samples comprise one or more cell lines.
14. (original) The method of claim 13, wherein expression of one or more genes in the one or more cell lines is artificially altered prior to treating with a member of a compound library using a procedure selected from the group consisting of: insertional mutagenesis, deletion of genomic DNA, targeted gene disruption, transcription blocking, introduction of a genomic or episomal vector, antisense DNA or RNA, ribozymes, iRNA, DNA binding oligonucleotides, and zinc finger proteins.
15. (original) The method of claim 1, wherein the biological samples comprise eukaryotic samples.
16. (original) The method of claim 1, wherein the biological samples comprise prokaryotic samples.
17. (original) The method of claim 1, wherein the compound library comprises one or more of: a compound collection library, a combinatorial chemical library, a scaffold-focused chemical library, a target focused chemical library, an antibody library, a biological library, a natural product library, an antisense agent library, an iRNA library, a siRNA library, a ribozyme library, a peptide library, and a combinatorial nucleic acid oligomer library.
18. (original) The method of claim 1, comprising obtaining expressed RNA samples from at least 500 biological samples, each of which biological samples is treated with a different member of a compound library.
19. (original) The method of claim 1, comprising obtaining expressed RNA samples from at least 1000 biological samples, each of which biological samples is treated with a different member of a compound library.

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20. (original) The method of claim 1, comprising obtaining expressed RNA samples from at least 10,000 biological samples, each of which biological samples is treated with a different member of a compound library.
21. (original) The method of claim 1, comprising obtaining the one or more expressed RNA samples by isolating total cellular RNA.
22. (original) The method of claim 1, comprising obtaining the one or more expressed RNA samples by isolating messenger RNA (mRNA).
23. (cancelled)
24. (currently amended) The method of claim ~~1~~ 23, comprising arraying a plurality of amplified nucleic acids corresponding to the plurality of expressed RNA samples, which amplified nucleic acids are produced by selective amplification of the plurality of expressed RNA samples.
25. (original) A method for simultaneously quantitating a plurality of expression products from a plurality of biological samples, the method comprising:
- (a) providing at least one nucleic acid array comprising a plurality of amplified nucleic acids corresponding to a plurality of expressed RNA samples, each obtained from a biological sample, which amplified nucleic acids are produced by selective amplification of the plurality of expressed RNA samples;
  - (b) hybridizing a plurality of defined sequence probes, which defined sequence probes each comprise a different polynucleotide sequence, and which probes are each capable of generating a different detectable signal, to the nucleic acid array; and,
  - (c) detecting hybridization to each of the plurality of defined sequence probes.
26. (original) The method of claim 24 or 25, wherein the amplified nucleic acids are produced by selective amplification by one or more method selected from the group consisting of: PCR, TMA, NASBA, and RCA.
27. (original) The method of claim 24 or 25, wherein the selective amplification is performed by PCR.

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28. (original) The method of claim 24 or 25, wherein the selective amplification is performed by multiplex PCR using a plurality of gene specific primers.
29. (original) The method of claim 28, wherein the gene specific primers further comprise a universal priming sequence.
30. (original) The method of claim 24 or 25, wherein the amplification products are pooled for arraying.
31. (original) The method of claim 24 or 25, wherein the selective amplification amplifies between about 5 and about 100 polynucleotide sequences.
32. (original) The method of claim 24 or 25, wherein the selective amplification amplifies between about 10 and about 50 polynucleotide sequences.
33. (original) The method of claim 24 or 25, comprising amplifying each expressed RNA sample in two or more target specific amplification reactions and spatially arraying the resulting amplification products in two or more locations on an array.
34. (original) The method of claim 33, comprising hybridizing a plurality of probes each of which specifically hybridizes to the products of a different target specific amplification reaction.
35. (previously presented) The method of claim 1 or 25, wherein the plurality of defined sequence probes comprises at least a first defined sequence probe and at least a second defined sequence probe, which first defined sequence probe hybridizes to a housekeeping gene and which at least second defined sequence probe hybridizes to a target sequence; and wherein step (e) of claim 1 or step (c) of claim 25 further comprises determining the detectable signal of the at least second defined sequence probe relative to the detectable signal of the first defined sequence probe.
36. (original) The method of claim 35, wherein the nucleic acids corresponding to the expressed RNA samples are arrayed in two or more duplicate arrays, and each array is hybridized to the first defined sequence probe and the least a second defined sequence probe, wherein the first defined sequence probe is the same between the two or more duplicate

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arrays and the at least second defined sequence probe differs between the two or more duplicate arrays.

37. (original) The method of claim 1 or 25, wherein plurality of defined sequence probes comprises set of genes comprising disease related targets.

38. (original) The method of claim 1 or 25, comprising arraying the nucleic acids on a solid phase surface.

39. (original) The method of claim 38, comprising arraying the nucleic acids on a two dimensional solid phase surface.

40. (original) The method of claim 38, comprising arraying the nucleic acids on a plurality of solid phase surfaces.

41. (original) The method of claim 40, wherein the plurality of solid phase surfaces are selected from the group consisting of: beads, spheres and optical fibers.

42. (original) The method of claim 38, wherein the solid phase surface comprises a material selected from the group consisting of: glass, coated glass, silicon, porous silicon, nylon, ceramic and plastic.

43. (original) The method of claim 1 or 25, wherein the defined sequence probes comprise one or more synthetic probes selected from the group consisting of: an oligonucleotide, a cDNA; an amplification product, and a restriction fragment.

44. (original) The method of claim 1 or 25, wherein the defined sequence probes capable of generating a detectable signal comprise one or more of: a fluorescent label, a chromophore, an electrophore, a radioactive nuclide, a chemically reactive moiety, an amplifiable signal element and a ligand capable of binding to an enzyme.

45. (original) The method of claim 44, wherein the amplifiable signal element is an oligonucleotide.

46. (original) The method of claim 45, wherein at least one of the plurality of defined sequence probes comprising an amplifiable signal element is detected by one or more of branched DNA amplification (BDA), rolling circle amplification (RCA), hybridization signal

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amplification method (HSAM), ramification amplification method (RAM) and a DNA dendrimer probe.

47. (previously presented) The method of claim 44, wherein at least one of the plurality of defined sequence probes comprises an amplifiable signal element, which amplifiable signal element comprises a ligand which binds to a second amplifiable signal element.

48. (original) The method of claim 44, wherein the amplifiable signal element comprises an enzyme or a catalyst.

49. (original) The method of claim 1 or 25, further comprising amplifying at least one detectable signal prior to detecting hybridization to the plurality of labeled probes.

50. (original) The method of claim 1 or 25, further comprising comparing the detected hybridization between samples.

51-57. (cancelled)